of IL12, which is far higher in XCR1+ DCs than in other DC types, may also be important. It is also likely that XCR1+ DCs express a unique set of chemokines and chemokine receptors, maybe including XCR1 itself, that determines their function. It will be important to investigate how this new model for T cell help applies to other CD8+ T cell responses, including anti-tumor responses.

A key step for future research will certainly be to unravel the role of DC subpopulations during the initiation of immune responses in humans. Both T cell and DC lineage organizations are conserved between human and mice. However, in both cases, the functions of the subsets seem to have evolved differently. CD4+ human T cells are often cytotoxic, and it is still unclear if the human lineage homologs of XCR1+ DCs, which express BDCA3+ and CD141+, cross-present antigens more efficiently than other DC subsets. In addition, the production of IL-12 is clearly not restricted to the human CD141+ DCs. Determining which human DC, if any, functions as a "T cell help platform" will certainly be a major challenge in the next years and an essential step toward designing effective CD8+ T cell vaccines.

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Melatonin Lulling Th17 Cells to Sleep

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In this issue, Farez et al. report that the circadian hormone melatonin, whose levels vary with seasonal changes in night length, shifts the immune response toward an anti-inflammatory state that may explain the seasonal variability of multiple sclerosis disease activity.

An imbalance between the inflammatory and regulatory responses of the immune system can lead to chronic immune cell activation and autoimmunity. Mounting evidence implicates the Th17 subset of T helper cells, characterized by the production of the proinflammatory cytokine interleukin-17 (IL-17), with playing a central role in autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease (IBD) (Gaffen et al., 2014). Predominantly located at barrier tissues that interface with the external world, Th17 cells maintain a high degree of flexibility to respond rapidly to constant fluctuations in environmental conditions and stimuli. The mechanisms that allow the adaptation of Th17 cells to the ever-changing environment include the ability to respond to changing nutrient status through the aryl hydrocarbon receptor (AHR) (Quintana et al., 2008), to oxygen sensing pathways including HIF1α (Dang et al., 2011), and to changes in osmotic pressure through serum/glucocorticoid regulated kinase 1 (SGK1) (Wu et al., 2013). In this issue of *Cell*, Farez et al. (2015) uncover another environmental cue—seasonal changes in daylight—that modulates the development of pathogenic Th17 cells. The daylight effect is mediated by the hormone melatonin, produced by the pineal gland and involved in the regulation of the circadian rhythm (Brzezinski, 1997). Melatonin inhibits the development of proinflammatory Th17 cells and shifts the balance of the immune response toward immunosuppression.

It has been known for some time that the latitudinal gradient—the greater the distance from the equator— correlates with increasing occurrence of multiple sclerosis (Alonso and Hernán, 2008). One of the phenomena linked to latitude is seasonal variation in exposure to UV radiation. There are convincing epidemiological data supporting the role of UV radiation-dependent vitamin D in reducing the disease course of MS (Munger et al., 2004). Yet, this correlation does not explain the increase in MS

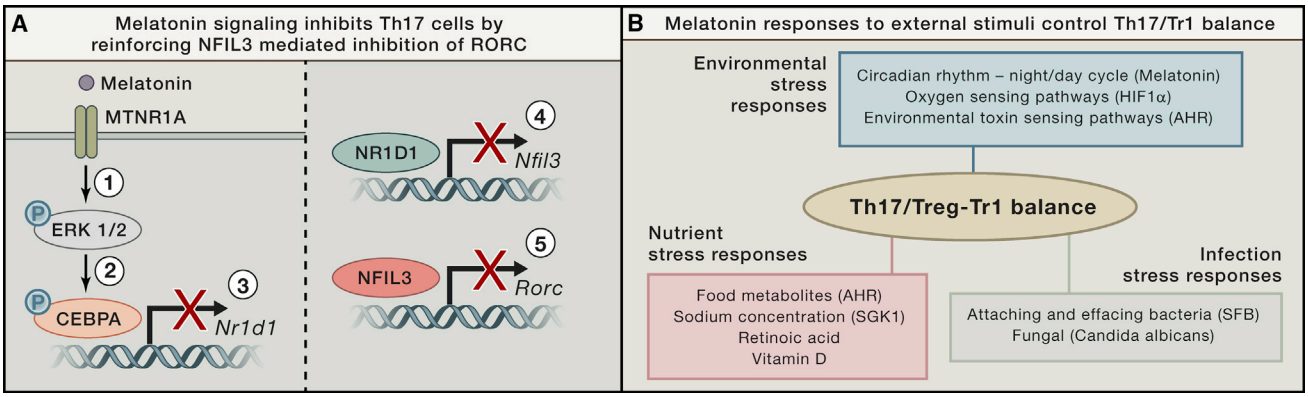

Figure 1. Melatonin Shifts the Balance from Th17 to Tr1

(A) Depicted is a schematic of the melatonin signaling pathway resulting in the inhibition of *Rorc*. (1) Melatonin signals through the melatonin receptor MTNR1A and results in ERK 1/2 phosphorylation. (2) Phosphorylated ERK 1/2 activates the transcription factor C/EBPα (3) and represses the expression of *Nr1d1* (REV-ERBα). (4) NR1D1 represses the transcription of *Nfil3*, which is a (5) repressor of *Rorc*. Thus, melatonin signaling releases the inhibition of Nfil3 by NR1D1 and results in the suppression of *Rorc*.

(B) A representation of various environmental cues regulating the balance between proinflammatory Th17 cells and immunosuppressive Treg/Tr1 cells.

relapse rates during spring and summer months, when UV rays are most abundant. In order to understand the environmental factors impacting the seasonal pattern of MS relapses, Farez et al. (2015) hypothesize that melatonin production, which also follows seasonal variation, may be involved in MS disease. Following up on a cohort of MS patients, the authors identify a negative correlation between clinical relapse and melatonin levels, with the highest levels of melatonin and the lowest exacerbation rate during the winter months. Indeed, serum from relapsing-remitting MS patients shows a negative correlation between the levels of melatonin and the proinflammatory cytokine IL-17 and a positive correlation with the anti-inflammatory cytokine IL-10. In vitro, the addition of melatonin suppresses the polarization of human T helper cells into the Th17 lineage, resulting in diminished expression of the Th17 master transcription regulator *RORC* and production of IL-17. In addition to its negative impact on Th17 differentiation, melatonin also enhances the polarization of type 1 regulatory cells (Tr1), which can suppress immune responses through the production of IL-10. Through a series of carefully designed experiments with mice genetically deficient in different components along the melatonin signaling pathway, the authors find that melatonin-dependent reinforcement of NFIL3, a negative regulator of *Rorc*, suppresses the development of Th17 cell in murine cells, while activation of RORα boosts the Tr1cell fate.

Melatonin signals through the membrane melatonin receptor (MTNR1A) that is expressed on a variety of cell types, including T cells. Both melatonin and the small molecule agomelatine, a MTNR1A agonist, repress the differentiation of murine Th17 cells in vitro, resulting in the suppression of key Th17 signature genes, *Rorc*, *Il17*, and *Il23r*. Importantly, T cells from MTNR1A KO mice are resistant to the suppressive impact of melatonin in Th17 cell differentiation, arguing that the membrane melatonin receptor is critical to mediate the effects of melatonin in Th17 cell polarization. What is the molecular mechanism of melatonin-dependent inhibition of Th17 cells? The key to answering this question is based on a previous report (Yu et al., 2013) demonstrating an important contribution of REV-ERBα, a transcriptional repressor with key regulatory functions in the control of the circadian cycle, in promoting Th17 cell development, thus linking the circadian clock with Th17 cell development. Here is where the story gets complicated. Melatonin increases the activation of Erk 1/2 which in turn leads to an increase in the phosphorylation of the transcription factor C/EBPα. C/EBPα binds to the promoter of *Nr1d1* (REV-ERBα) and acts as a negative regulator. Confirming the regulatory function of REV-ERBα in *Nfil3*, melatonin suppression of *Nr1d1* expression results in increased NFIL3 binding to the *Rorc* promoter, leading to reduced expression of *Rorc* (Figure 1A). In a complementary set of experiments, the authors find that melatonin signaling also enhances in vitro Tr1 cell polarization, increases IL-10 production, and boosts the suppressive ability of these cells. Melatonin increases binding of RORα to the *Il10* promoter, which synergizes with AHR and c-Maf to enhance *Il10* expression. Taken together, melatonin shifts the balance from pathogenic Th17 cells to favor the immunosuppressive Tr1 cells. Importantly, administration of melatonin in a mouse model of MS leads to amelioration of disease. Melatonin reduces the frequency of Th17 cells infiltrating the central nervous system, particularly the pathogenic IL-17-IFNγ and IL-17-GMCSF double-positive cells, while concomitantly increasing IL-10 producing immunosuppressive Tr1 cells in the mouse model.

Over the past 50 years, there has been a steady rise in the incidence of autoimmune diseases such as MS, RA, psoriasis, and IBD, particularly in developed countries. Recent studies have uncovered many environmental stress factors associated with the modern life contributing to the development of inflammatory disorders (Figure 1B). One example is the "high-salt" Western diet, where SGK1 on Th17 cells play a role in exacerbating T cell inflammatory mechanisms (Wu et al., 2013). It is tempting to speculate whether the invention of artificial

lights—which facilitates chronic circadian disruptions—could have contributed to an imbalance between the inflammatory and regulatory responses of the immune system, leading to immune dysregulation. The current study establishes a clear link between melatonin, a hormone involved in the regulation of the circadian rhythm, and the inhibition of proinflammatory Th17 cells, thereby shifting the balance of the immune response toward immunosuppression. These findings support the immunosuppressive properties of melatonin, as well as define the melatonin-NFIL3-RORγt pathway as a potential therapeutic target for the treatment of MS.

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The Touching Tail of a Mechanotransduction Channel

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In mechanotransduction, sensory receptors convert force into electrical signals to mediate such diverse functions as touch, pain, and hearing. In this issue of *Cell*, Zhang et al. present evidence that the fly NompC channel senses mechanical stimuli using its N-terminal tail as a tether between the cell membrane and microtubules.

As far back as Aristotle, the sense of touch was valued, along with hearing, sight, smell, and taste, as one of the "five outward wits" central to the human experience. It is now clear that "touch" is not merely a core aspect of perception but represents a highly specialized, diverse, and complex series of sensory systems. Mechanosensation plays an important role not just in feeling objects and textures but also in eliciting pain or pleasure, detecting sounds, and sensing balance and the position of our own bodies. In this issue of *Cell*, Zhang et al. (2015) explore the molecular mechanisms of mechanosensory transduction, a process in which molecules in cell membranes convert mechanical forces into electrical signals (Zhang et al., 2015). They present a strong case that the *Drosophila* NompC ion channel senses mechanical stimuli using its N-terminal tail as a tether between the cell membrane and the microtubules of the cytoskeleton (Figure 1).

Although numerous mechanosensing ion channels have been identified, the mechanisms by which force-to-signal conversions occur remain unclear in many cases (Anishkin et al., 2014). The rapid activation kinetics of mechanosensing channels, seemingly too rapid for second messenger generation, suggests they are gated directly by mechanical forces acting on the plasma membrane. Two non-exclusive models for force-activation of channels have been proposed. In the membrane force model, pressure on the plasma membrane alters its shape and/or surface area, causing opening of the embedded protein channel. On the other hand, the tether model posits that molecular tethers convey force between the channel and the cytoskeleton or extracellular milieu. Although several examples of membrane force-activated channels exist, notably the bacterial MscL channel, there has been no direct molecular evidence supporting a tether model (Anishkin et al., 2014).

Zhang et al. (2015) focus on the *Drosophila* Transient Receptor Potential (TRP) channel NompC. Cation channels of the TRP family have long been